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Synthesis of 2-bromomethyl-2,3-dihydrobenzofurans from 2-allylphenols enabled by organocatalytic activation of *N*-bromosuccinimide†

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2-Bromomethyl-2,3-dihydrobenzofurans are valuable and highly functionalized compounds that can be obtained by an intramolecular reaction between 2-allylphenols and a bromenium ion source (Br^+). Due to the ineffectiveness of the safe and easy-to-handle brominating agent *N*-bromosuccinimide (NBS) to deliver the desired products, a catalytic process using a mixture of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and acetic acid was conceived. We hypothesized that this catalytic system delivers *in situ* acetyl hypobromite (AcOBr) as the active brominating agent, enabling the conversion of a range of 2-allylphenols with diverse electron densities to the products. The protocol was robust enough to permit the reaction to be scaled up to 10 mmols of starting material. Besides, the functional group interconversion with a 2-bromomethyl-2,3-dihydrobenzofuran derivative was successfully demonstrated.

Introduction

Naturally occurring compounds represent an unlimited source of inspiration for chemists to construct novel substances in order to meet the increasing demands of society. The 2,3-dihydrobenzofuran (2,3-DHB) core, for instance, is found in many biologically active small organic molecules. Therefore it is acknowledged as a privileged scaffold for the design of bio-inspired drugs.[1] The structures of some of these compounds and their respective biological activities are exemplified in Fig. 1.[2]

Not surprisingly, research into efficient methodologies to produce 2,3-DHB derivatives has been constantly explored.[3] In particular, the synthesis of 2-halomethyl-2,3-dihydrobenzofurans is very appealing as it allows the preparation of highly functionalized and versatile compounds. Halogenated organic compounds themselves stand up as a very important class of substances. They find broad applicability as commodities for synthetic transformations, pharmaceuticals, agrochemicals, *etc.*[4] In this context, carbohalogenation of allyl phenyl ethers under different reaction conditions is a consolidated methodology for the synthesis of halogenated analogues of 2,3-DHB (Scheme 1a). Typical reaction conditions in this strategy include: (i) use of metal catalysts; (ii) generation of radical precursors or (iii) radicalar photo-induced processes.[5] In common, all these require the utilization of starting materials assembled with a responsive organic functionality in the *ortho* position with respect to the ether moiety (*e.g.* halogens, amines, *etc.*).

Another approach for the preparation of halogenated 2,3-DHB involves the use of elemental halogens in the oxyhalogenation of 2-allylphenols (Scheme 1b).[6] This strategy stems from the premise that the reaction between a halenium ion source (X^+; where X = Cl, Br or I) and an alkene delivers a haliranium ion, which can be intramolecularly attacked to produce a cyclic product.[7,8] In the past few years, much effort has been devoted toward the monohalogenation of alkenes. Perhaps the most studied transformations are the intramolecular halolactonization and haloetherification of organic substrates employing haloimide-based reagents (*e.g.*, *N*-halosuccinimide, *N*-halophthalimide, *etc.*). This

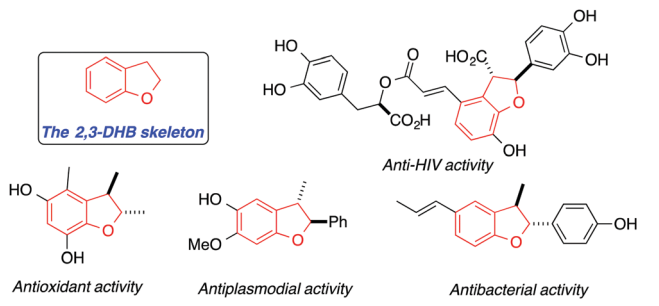

Fig. 1 Representative 2,3-dihydrobenzofurans and their biological activities.

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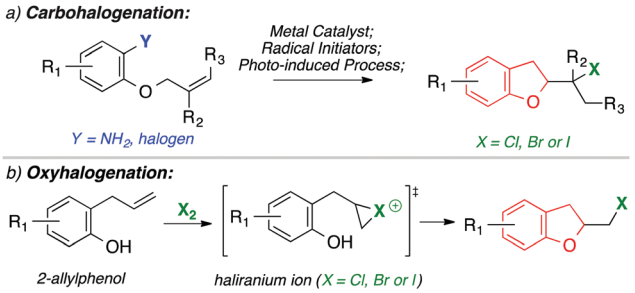


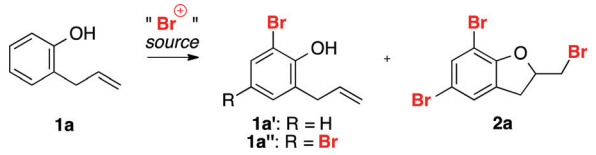
Scheme 1 Carbohalogenation and oxyhalogenation of alkenes as strategies for the synthesis of 2-halomethyl-2,3-DHB.

strategy represents a powerful tool to produce highly functionalized organic compounds from alkenes.[9] Accordingly, and taking into account the limitations of the previous methods for the preparation of halogenated 2,3-DHB, including the use of metal catalysts (carbohalogenation) or highly hazardous elemental halogens in the oxyhalogenation, herein we would like to report our contribution to the synthesis of these molecules with numerous and important applications. In our approach 2-bromomethyl-2,3-dihydrobenzofurans were obtained by the oxybromination of 2-allylphenols with *N*-bromosuccinimide (NBS), a safe, inexpensive and reliable reagent for the electrophilic bromination of organic substrates. It is noteworthy that the product formation could be achieved only in reactions using an organocatalyst to activate NBS. Among a set of catalysts screened, we have found that a combination of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and acetic acid was the ideal to such a task. The designed experiments lead us to strongly suggest that acetyl hypobromite (AcOBr) might be the active brominating agent of the process.

Results

It is extensively reported in the literature that Brønsted or Lewis bases activate *N*-haloimides, accelerating the halogenation of organic substrates.[9] Considering our previous contribution on this topic,[10] we have started the present study employing a catalytic amount of 4-dimethylaminopyridine (DMAP), NBS and 2-allylphenol **1a** in order to produce the brominated 2,3-dihydrobenzofuran core by a bromiranium-induced cyclization step. It was observed that the use of one or two equivalents of NBS resulted exclusively in the bromination of the phenol ring of **1a** (Table 1, entries 1 and 2).[11] In order to achieve the intramolecular cyclization step, at least three equivalents of NBS were required, allowing the formation of 2-bromomethyl-2,3-dihydrobenzofuran **2a** in 57% yield after 2 hours of reaction (entry 3). Surprisingly, when **1a** was treated with 3 equivalents of bromine, a complex mixture of products was observed (entry 4). The use of a mixture of a bromide salt, hydrogen peroxide and a catalytic amount of PhTeTePh to produce *in situ* the brominating agent necessary for product formation was also evaluated.[12] Albeit being considered a process with a lower impact on the environment compared to the use of NBS, only a small amount of product **2a** could be obtained using this protocol, even after 24 hours of reaction (entry 5).

Table 1 Initial assessment for the oxybromination of **1a**

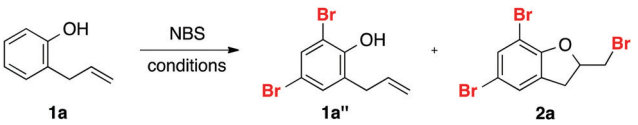


Entry	Reaction conditions	Yield[a] 1a′	1a″	2a
1[b]	DMAP (10 mol%)/NBS (1.0 equiv.)	47	19	0
2[b]	DMAP (10 mol%)/NBS (2.0 equiv.)	0	76	0
3[b]	DMAP (10 mol%)/NBS (3.0 equiv.)	0	0	57
4[c]	Br_2 (3.0 equiv.)	Complex mixture		
5[d]	PhTeTePh (0.1 mol%)/LiBr (3.6 equiv.)/H_2O_2 (3.6 equiv.)	0	55	8

[a] Product yields and distribution determined by ^{1}H NMR after purification by a chromatographic column. [b] Solvent = DCM/AcOH 10/1 (0.18 M final concentration), and 2 hours in the dark (amber flask wrapped with an aluminium foil) at 20 ± 2 °C (water bath). [c] Solvent = DCM (0.025 M final concentration), and 20 minutes in the dark (amber flask wrapped with an aluminium foil) at 20 ± 2 °C (water bath). [d] Solvent = 1,4-dioxane/AcOH 4/1 (0.2 M final concentration), and 24 hours at 20 ± 2 °C (water bath).

Subsequently, a set of catalysts and solvents were screened in order to find the best reaction conditions to promote the conversion of **1a** to **2a** (Table 2). To facilitate the formation of the cyclic product, all the experiments were conducted employing 3.3 equivalents of NBS. Accordingly, after 30 minutes of reaction using 10 mol% of DMAP as the catalyst in a mixture of DCM and AcOH, **2a** was obtained in 55% yield along with 13% of **1a**″ (entry 1). If the catalyst was removed from the reaction mixture, no conversion of **1a** to products could be observed at all (entry 2). Pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO)

Table 2 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	1a″[b] (%)	2a[b] (%)
1	DMAP	DCM/AcOH (10/1)	13 ± 2	55 ± 1
2	None	DCM/AcOH (10/1)	0 ± 0	0 ± 0
3	Pyridine	DCM/AcOH (10/1)	12 ± 1	58 ± 4
4	DABCO	DCM/AcOH (10/1)	42 ± 3	20 ± 2
5	DBU	DCM/AcOH (10/1)	14 ± 3	69 ± 2
6	Ph_3P	DCM/AcOH (10/1)	2 ± 2	40 ± 2
7	Ph_3PS	DCM/AcOH (10/1)	0 ± 0	15 ± 2
8	Ph_3PSe	DCM/AcOH (10/1)	0 ± 0	10 ± 1
9[c]	DBU	DCM	31 ± 1	15 ± 2
10[d]	DBU	AcOH	52 ± 2	7 ± 2
11	DBU	MeCN/AcOH (10/1)	0 ± 0	0 ± 0
12	DBU	Acetone/AcOH (10/1)	0 ± 0	61 ± 2
13	DBU	Toluene/AcOH (10/1)	2 ± 1	58 ± 1

[a] Reaction conditions: **1a** (0.5 mmol), NBS (1.65 mmol), AcOH (0.25 mL), catalyst (10.0 mol%, relative to **1a**), undecane (internal standard, 0.25 mmol) and solvent (2.5 mL); 30 minutes in the dark (amber flask wrapped with an aluminium foil) at 20 ± 2 °C (water bath). [b] GC yield (average for duplicate runs). [c] Total volume of DCM = 2.75 mL. [d] Total volume of AcOH = 2.75 mL.

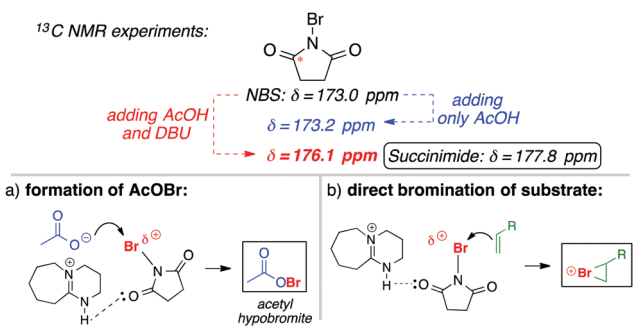
and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were also evaluated (entries 3–5). Among them, DBU showed the best result delivering product **2a** in 69% yield (entry 5). Lewis bases such as Ph_3P, Ph_3PS and Ph_3PSe were also tested (entries 6–8).[9] However, none of them has enhanced the result previously obtained with DBU. As the best catalyst for the desired transformation was found, we turned our attention to the solvent. Using exclusively DCM[13] or pure AcOH instead of a 10/1 mixture of DCM/AcOH, a drastic decrease of the reaction rate was observed (entries 9 and 10, respectively). Finally, the combination of acetic acid with other solvents was evaluated. Except for MeCN, which did not produce any detectable amount of brominated products, acetone and toluene gave **2a** in satisfactory yields (entries 11–13).

With the optimized reaction conditions in hand, control experiments were designed to better understand the reaction mechanism. Firstly, we decided to follow the chemical shift of the tagged-carbon of NBS by ^{13}C NMR under different circumstances (Scheme 2). For this, $CDCl_3$ solutions containing a 1/1/1 mixture of NBS/AcOH/DBU or a 1/1 mixture of NBS/AcOH were screened. Only when AcOH and DBU were added, an important deshielding of the carbon signal could be observed, approaching the chemical shift of the corresponding carbon atom on succinimide. This indicates that at least a partial transfer of the bromine atom of NBS and consequently protonation of the resultant succinimide anion was taking place. Thus, and considering all the collected data up to this point, at least two distinct scenarios would be plausible to explain the bromination of the substrate **1a**: *in situ* formation of the strong brominating agent acetyl hypobromite (AcOBr)[14] as depicted on Scheme 2a; or direct bromination of the substrate, due to activation of NBS by hydrogen-bonding with protonated DBU (Scheme 2b).[15] Unfortunately, none of these scenarios could be ruled out by the ^{13}C NMR experiments.

To shed light on this conundrum and better understand the reaction mechanism, further experiments were proposed (Table 3). Firstly, we replaced AcOH by TFA, an acid with a non-nucleophilic conjugate base to disfavor the pathway described in Scheme 2a. Conversely, this change in the reaction condition should not impact the product formation if the pathway depicted on Scheme 2b is the predominant one to produce **2a**. Quite surprisingly, when a DBU/TFA mixture was used, after four hours of reaction **2a** could not be detected,[16] compound **3** being the major brominated product obtained. This is in sharp contrast to the formation of **2a** employing the DBU/AcOH mixture (Table 3, entries 1 and 2).[17] The same product **3** was obtained using exclusively TFA as the reaction additive (entry 3). The formation of the product **3** should be therefore the result of the action of a different brominating agent or perhaps, a different kind of activation of *N*-bromosuccinimide. It has been reported in the literature that even small structural changes on a given catalyst employed for activation of NBS can account for a drastic change in the regio- and chemoselectivity of the product.[18] Furthermore, albeit less common, the activation of NBS with Brønsted acids has been described in the literature. Accordingly, only strong acids (*e.g.* TFA, and sulfuric or phosphoric acid derivatives) are able to activate NBS by protonation.[19] We believe that this is the case in the reaction with TFA and no added DBU (Table 3, entry 3). On the other hand, in the presence of the base, the trifluoroacetate anion is generated. Previous reports in the literature have postulated the involvement of trifluoroacetate hypobromite (F_3CCO_2Br) as the brominating agent, though it has been prepared under reaction conditions different than ours.[20]

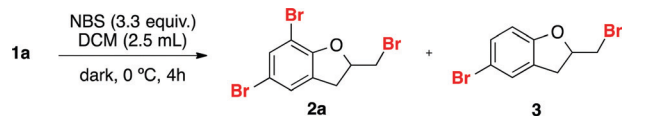
These previous results arouse the assumption that the acetate ion has an important role in the reaction outcome, probably due to the formation of the brominating agent acetyl hypobromite as depicted in Scheme 2a.[21] This hypothesis was further supported by the replacement of DBU by Cs_2CO_3. In this case, the inorganic base would still produce acetate ions in the reaction mixture but would not be able to afford a hydrogen-bond donor species to activate NBS (as illustrated in Scheme 2b). Albeit **2a** was obtained in a lower yield, the reaction using a Cs_2CO_3/AcOH combination showed that like the DBU/AcOH mixture, the same brominating agent was being generated once the product **2a** was selectively formed (entry 4). Finally, it was observed that experiments conducted in the dark or under oxygen-free conditions and exposed to daylight gave essentially the same yields of **2a**: 71% and 68%, respectively (entries 1 and 5) suggesting that the reaction occurs mainly by an ionic pathway.

Considering these evidences, a plausible reaction mechanism is described in Scheme 3. Initially an acid–base reaction takes place between DBU and acetic acid. The soluble acetate ion formed reacts with NBS to deliver acetyl hypobromite, the



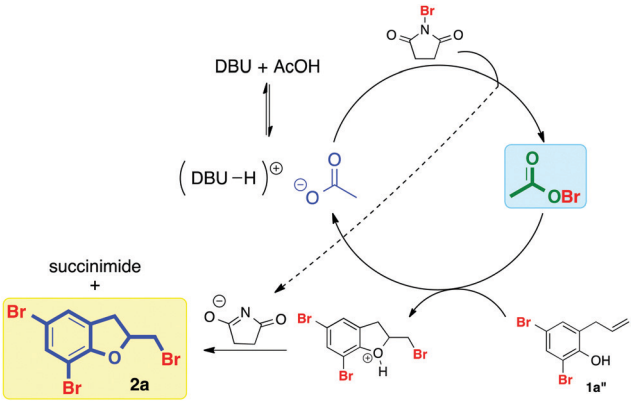
Scheme 2 Experiments investigating the reaction mechanism.

Table 3 Effects of the reaction conditions on the bromination of **1a**[a]

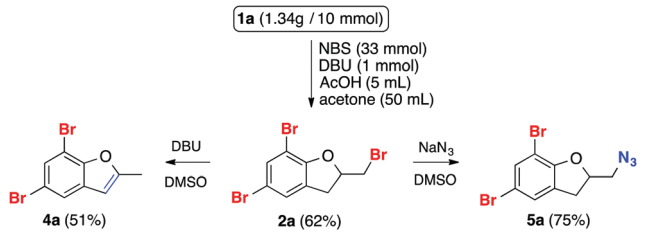


Entry	Reaction conditions	**2a**[b] (%)	**3**[b] (%)
1	DBU (10 mol%), DCM/AcOH (10/1)	71 ± 2	0
2	DBU (10 mol%), DCM/TFA (10/1)	0	44 ± 3
3	DCM/TFA (10/1)	0	33 ± 2
4	Cs_2CO_3 (10 mol%), DCM/AcOH (10/1)	43 ± 1	0
5	DBU (10 mol%), DCM/AcOH (10/1), sun light, and O_2-free	68 ± 1	0

[a] Reactions were performed during 4 hours, in the dark (amber flask wrapped with an aluminium foil) at 0 ± 1 °C (ice bath). [b] Yield of pure isolated products.

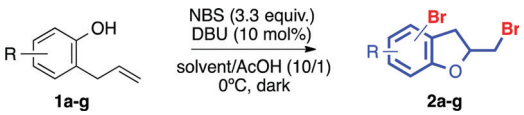


Scheme 3 Plausible reaction mechanism.



Scheme 4 Scale-up of the reaction for formation of **2a** and its derivatization.

Table 4 Substrate scope for synthesis of brominated 2,3-dihydrobenzofuran **2**[a]



Entry	Substrate	Product	Time (h)	Yield (%)
1	**1a**	**2a**	3	79
2	**1b**	**2b**	3	83
3	**1c**	**2c**	3	82
4[b]	**1d**	**2d**	0.25	31
5	**1e**	**2e**	3	56
6[b]	**1f**	**2f**	24	68
7[b]	**1g**	**2g**	6	10

[a] Reaction conditions: starting material (1.0 mmol), DBU (0.1 mmol), NBS (3.3 mmol), AcOH (0.5 mL) and acetone (5.0 mL) at 0 °C (ice bath) in the dark (an aluminum foil). Yields reported for pure isolated products. [b] Reaction using DCM as solvent (5.0 mL).

active brominating agent in the system. As AcOBr is generated, it initially brominates twice the phenol ring of **1a** producing **1a″**. Then, AcOBr transfers the bromine atom to the alkene moiety of **1a″**, regenerating the acetate ion and delivering a protonated cyclic intermediate. The final product **2a** is obtained after proton abstraction by the succinimide anion.

To verify the substrate scope and limitations, experiments with a broader range of substituted 2-allylphenols were conducted under the optimized conditions. For most substrates it was possible to replace DCM by acetone, thus avoiding the use of this strongly regulated chlorinated solvent. A three-hour reaction with **1a** produced the 2-bromomethyl-2,3-dihydrobenzofuran **2a** in 79% yield (Table 4, entry 1). Alkylated derivatives such as **2b** and **2c** were also efficiently obtained in 83% and 82% yields, respectively. Although in these substrates it would be possible to introduce just one bromine atom into the aromatic ring, reactions with 2.2 equivalents of NBS were incomplete after 3 hours as judged by TLC. When the strongly activated substrate **1d** was employed, the reaction was completed within 15 minutes. Despite our attempts to improve the reaction yield for this product, including the use of DCM as solvent, only 31% of **2d** could be obtained. Substrates bearing slight or moderate electron withdrawing groups, such as **1e** and **1f** were smoothly converted to the brominated products **2e** and **2f**. On the other hand, no cyclization product was obtained with the substrate **1g**. In this case, the intermolecular addition of acetate on the bromiranium ion prevailed, producing **2g** in 10% yield along with a complex mixture of products (formation of the 2,3-dihydrobenzofuran derivative was not observed).

Then, we investigated if a scale-up of the reaction for the formation of **2a** would be feasible. Accordingly, a preparative reaction was successfully performed using 10 mmol of **1a**, delivering the product **2a** in 62% isolated yield (Scheme 4).[22] Lastly, derivatizations of the compound **2a** were proposed. For instance it was converted to the benzofuran derivative **4a**, a framework commonly observed in naturally occurring compounds,[23] or to the chemically versatile azide **5a**.

Conclusions

To summarize, in this contribution we have described a simple and straightforward method to produce 2-bromomethyl-2,3-dihydrobenzofurans. These valuable and highly functionalized compounds were obtained as the result of a bromiranium-induced cyclization

step in the reaction between 2-allylphenols and *N*-bromosuccinimide (NBS). It is noteworthy that the use of NBS showed much better results compared to other well-established brominating agents or protocols, such as the use of elemental bromine or the catalytic activation of H_2O_2 for the oxidation of bromide salts (bromoperoxidase-like process). Nevertheless, NBS itself was ineffective to produce the desired product in a reasonable rate; in order to obtain products efficiently, activation of NBS was required. We have found that a catalytic process using a combination of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and acetic acid was ideal to such a task. Designed experiments indicated that this catalytic system resulted in the *in situ* production of acetyl hypobromite (AcOBr), supposedly the active brominating agent of the process. Finally, the substrate scope could be extended to include 2-allylphenols with a diverse range of electron densities and the scale up of the reaction and derivatization of the product were successfully demonstrated.

Experimental section

General remarks

All commercial reagents were used as received. Solvents were of analytical grade and purified before use. Moisture-sensitive liquids were transferred using an airtight glass syringe through a rubber septum and stored under argon. Nuclear magnetic resonance (NMR) spectra were determined on a Bruker DPX-200 or a DRX-400 spectrometer. Chemical shifts (δ) are related in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Tetramethylsilane (TMS) was used as the internal reference standard for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. For some reactions their progress was followed by GC on a Shimadzu GC 2010-Plus, column RTx@RMS (30 m × 0.25 mm × 0.25 μm) using undecane (0.5 equivalent to substrate) as the internal standard. The GC product yields were calculated by the determination of the product concentration in the final reaction solutions using calibration curves obtained with authentic product samples and undecane as the internal standard. Melting points are uncorrected. All the starting materials used in this study (2-allylphenols) are known compounds and were prepared according to previous reports: **1a**, **1c**, **1e** and **1f**,[3a] **1b**,[24] **1d**,[25] and **1g**.[26]

Reaction of 1a with 1.0–3.0 equivalents of NBS catalyzed by DMAP

An amber screw-capped 3 dram vial, wrapped with aluminium foil, was charged with 2-allylphenol **1a** (67 mg, 0.5 mmol), DCM (2.5 mL), glacial acetic acid (0.25 mL), DMAP (4-dimethylamino-pyridine) (6.1 mg, 10.0 mol%, related to **1a**) and then *N*-bromosuccinimide (89.0 mg, 0.5 mmol; 178.0 mg, 1.0 mmol or 267.0 mg, 1.5 mmol). The reaction was performed at 20 ± 2 °C (the reaction vessel was immersed in a water bath). No precautions were taken to exclude oxygen or water from the reaction media. After two hours, the reaction mixture was diluted with 20 mL of DCM and washed with 2 M $NaHSO_3$ (2 × 20 mL) and water (1 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The products were purified by silica gel chromatography (hexanes) and their distribution determined by ^{1}H NMR. Mixtures of **1a′** and **1a″** or products **1a″** and **2a** were observed as described in Table 1 (entries 1–3). Characterization data of **1a″**: pale yellow oil; RMN ^{1}H ($CDCl_3$, 400 MHz) δ: 7.44 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 1.4 Hz, 1H), 5.97–5.87 (m, 1H), 5.57 (s, 1H), 5.12–5.08 (m, 2H), 3.38 (d, J = 6.5 Hz, 2H); RMN ^{13}C ($CDCl_3$, 100 MHz) δ: 149.7, 135.3, 132.6, 132.1, 129.8, 117.2, 112.7, 111.1, 34.9.

Reaction of 1a with Br_2

An amber screw-capped 3 dram vial, wrapped with aluminium foil, was charged with 2-allylphenol **1a** (67 mg, 0.5 mmol), DCM (20 mL) and then bromine (77.0 μL, 1.5 mmol). The reaction was performed at 20 ± 2 °C (the reaction vessel was immersed in a water bath). No precautions were taken to exclude oxygen or water from the reaction media. After 20 minutes, the reaction mixture was washed with $NaHSO_3$ 2 M (2 × 20 mL) and water (1 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford a complex mixture of products as described in Table 1 (entry 4).

Reaction of 1a with LiBr and H_2O_2

A 10 mL one-neck round-bottom flask was charged with LiBr (0.16 g, 1.8 mmol), 1,4-dioxane (2 mL) and glacial acetic acid (0.5 mL). After stirring for five minutes, 2-allylphenol **1a** (67 mg, 0.5 mmol) was added, followed by 8.8 M H_2O_2 (204 μL, 1.8 mmol) and PhTeTePh (0.10 mol% related to **1a**: 40 μL of a freshly prepared 12 mM solution in 1,4-dioxane). The reaction was performed at 20 ± 2 °C (the reaction vessel was immersed in a water bath). No precautions were taken to exclude oxygen or water from the reaction media. After 24 hours of reaction, it was diluted with distilled water (20 mL) and the products extracted with AcOEt (3 × 10 mL). The organic phase was washed with 2 M Na_2CO_3 (2 × 10 mL), 2 M $NaHSO_3$ (2 × 10 mL) and water (1 × 10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Purification was performed by silica gel chromatography (hexanes) to afford a mixture of **1a″** and **2a** as described in Table 1 (entry 5).

Optimization of the reaction of 2-allylphenol 1a with NBS

An amber-screw capped 3 dram vial, wrapped with aluminium foil, was charged with 2-allylphenol **1a** (67 mg, 0.5 mmol), solvent (2.5 mL), glacial acetic acid (0.25 mL), catalyst as described in Table 2 (10.0 mol%, related to **1a**), undecane as an internal standard (53 μL, 0.25 mmol) and then *N*-bromosuccinimide (294 mg, 1.65 mmol). The reaction was performed at 20 ± 2 °C (the reaction vessel was immersed in a water bath). No precautions were taken to exclude oxygen or water from the reaction media. After 30 minutes, the reaction was quenched with $NaHSO_3$ 2 M (1 mL). The organic phase was separated, dried over $MgSO_4$, filtered and injected into a GC. The reported yields represent an average of duplicate runs.

Experiments for investigation of the mechanism

NMR experiments (Scheme 2)

NMR tubes were charged with NBS (27 mg, 0.15 mmol), $CDCl_3$ (600 μL), AcOH (9.0 μL, 0.15 mmol) and when applicable DBU (22.0 μL, 0.15 mmol). All the spectra were recorded on a Bruker DRX-400 spectrometer.

Reaction of 2-allylphenol 1a with DBU or Cs_2CO_3 and NBS (Table 3, entries 1 and 4)

An amber-screw capped 3 dram vial, wrapped with aluminium foil, was charged with 2-allylphenol **1a** (34 mg, 0.25 mmol), DCM (2.5 mL), glacial acetic acid (0.125 mL), DBU (3.8 μL, 10.0 mol%, related to **1a**) or Cs_2CO_3 (8.2 mg, 10.0 mol%, related to **1a**) and *N*-bromosuccinimide (147 mg, 0.825 mmol). The reaction was performed at 0 ± 1 °C (the reaction vessel was immersed in an ice bath). No precautions were taken to exclude oxygen or water from the reaction media. After 4 hours the reaction was diluted with 20 mL of DCM and washed with 2 M $NaHSO_3$ (2 × 20 mL) and water (1 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Products were purified by silica gel chromatography (hexanes/AcOEt = 95/5) to afford 65.5 mg, 71% yield of **2a** in the reaction with DBU (entry 1) or 39.7 mg, and 43% yield of **2a** in the reaction with Cs_2CO_2 (entry 4).

Reaction of 2-allylphenol 1a with DBU/TFA and NBS (Table 3, entry 2)

An amber screw-capped 3 dram vial, wrapped with aluminium foil, was charged with 2-allylphenol **1a** (34 mg, 0.25 mmol), DCM (2.5 mL), TFA (trifluoracetic acid) (0.125 mL), DBU (3.8 μL, 10.0 mol%, related to **1a**) and *N*-bromosuccinimide (147 mg, 0.825 mmol). The reaction was performed at 0 ± 1 °C (the reaction vessel was immersed in an ice bath). No precautions were taken to exclude oxygen or water from the reaction media. After 4 hours the reaction was diluted with 20 mL of DCM and washed with 2 M $NaHSO_3$ (2 × 20 mL) and water (1 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The products were purified by silica gel chromatography (hexanes/AcOEt = 95/5) to afford **3** as a white solid (32.1 mg, 44% yield); m.p. = 54–59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29–7.27 (m, 1H), 7.24–7.20 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.07–4.98 (m, 1H), 3.59 (dd, J^1 = 10.5 Hz, J^2 = 4.9 Hz, 1H), 3.51 (dd, J^1 = 10.5 Hz, J^2 = 6.7 Hz, 1H), 3.38 (dd, J^1 = 16.2 Hz, J^2 = 9.3 Hz, 1H), 3.13 (dd, J^1 = 16.2 Hz, J^2 = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.3, 131.1, 128.2, 128.0, 112.7, 111.0, 81.7, 34.32, 34.27; HRMS (APCI, positive mode) m/z calculated for $C_9H_8Br_2O$ $[M]^+$ 291.8916, found 291.8927. The experiment described in Table 3, entry 3 was performed in the same way but without the addition of DBU as the catalyst. In this reaction, 24 mg (33% yield) of **3** was obtained after purification.

Reaction of 2-allylphenol 1a with DBU/AcOH and NBS under O_2-free conditions (Table 3, entry 5)

An oven dried 10 mL two-neck round-bottom flask, was charged with 2-allylphenol **1a** (67 mg, 0. 5 mmol), DCM (5 mL), glacial acetic acid (0.25 mL) and DBU (7.5 μL, 10.0 mol%, related to **1a**). The reaction mixture was bubbled with argon for 10 minutes prior to the addition of *N*-bromosuccinimide (294 mg, 1.65 mmol). After 4 hours at 0 ± 1 °C (the reaction vessel was immersed in an ice bath) under argon and exposed to daylight, the reaction was diluted with 20 mL of DCM and washed with $NaHSO_3$ 2 M (2 × 20 mL) and water (1 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The products were purified by silica gel chromatography (hexanes/AcOEt = 95/5) to afford 125.5 mg, 68% yield of **2a**.

General procedure for the preparation of brominated products (Table 4)

An amber screw-capped 3 dram vial, wrapped with aluminium foil, was charged with 2-allylphenol **1** (1.0 mmol), acetone (5 mL), glacial acetic acid (0.5 mL), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (15 μL, 10.0 mol%, related to **1**) and then *N*-bromosuccinimide (587.4 mg, 3.3 mmol). The reaction was performed at 0 ± 1 °C (the reaction vessel was immersed in an ice bath). No precautions were taken to exclude oxygen or water from the reaction media. After the required reaction time had elapsed as judged by TLC, the reaction mixture was directly purified by silica gel chromatography.

Compound 2a. The general procedure was followed using **1a** (134.2 mg, 1.0 mmol). After 3 hours of reaction the product was purified by silica gel chromatography (hexanes) to afford **2a** as a white solid (293.0 mg, 79% yield); m.p. = 71–72 °C; RMN ^{1}H ($CDCl_3$, 400 MHz) δ: 7.41 (s, 1H), 7.21 (s, 1H), 5.14–5.07 (m, 1H), 3.64 (dd, J^1 = 10.5 Hz, J^2 = 4.2 Hz, 1H), 3.56–3.45 (m, 2H), 3.25 (dd, J^1 = 16.5 Hz, J^2 = 6.5 Hz, 1H), RMN ^{13}C ($CDCl_3$, 100 MHz) δ: 156.2, 133.7, 129.2, 127.2, 113.1, 103.4, 82.0, 35.4, 34.1; HRMS (APCI, positive mode) m/z calculated for $C_9H_7Br_3O$ $[M]^+$ 369.8021, found: 369.8029. For the gram scale experiment (Scheme 4) the general procedure was followed using **1a** (1.34 g, 10.0 mmol), acetone (50 mL), glacial acetic acid (5 mL), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (150 μL, 10.0 mol%, related to **1a**) and then *N*-bromosuccinimide (5.87 g, 33 mmol). After four days of reaction the product was purified by silica gel chromatography (hexanes) to afford **2a** as a white solid (2.28 g, 62% yield).

Compound 2b. The general procedure was followed using **1b** (190.3 mg, 1.0 mmol). After 3 hours of reaction the product was purified by silica gel chromatography (hexanes/AcOEt = 95/5) to afford **2b** as a yellow oil (288.9 mg, 83% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26 (s, 1H), 7.12 (s, 1H), 5.09–5.02 (m, 1H), 3.66 (dd, J^1 = 10.4 Hz, J^2 = 4.4 Hz, 1H), 3.53–3.43 (m, 2H), 3.23 (dd, J^1 = 16.0 Hz, J^2 = 6.4 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154. 2, 146.0, 128.2, 126.7, 121.2, 101.8, 81.5, 35.5, 34.4, 34.0, 31.6; HRMS (APCI, positive mode) m/z calculated for $C_{13}H_{16}Br_2O$ $[M]^+$ 347.9542, found: 347.9562.

Compound 2c. The general procedure was followed using **1c** (148.2 mg, 1.0 mmol). After 3 hours of reaction the product was purified by silica gel chromatography (hexanes/AcOEt = 98/2) to afford **2c** as a white solid (251.6 mg, 82% yield); m.p. = 46–49 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 (s, 1H), 7.06 (s, 1H), 5.03–4.94 (m, 1H), 3.59 (dd, J^1 = 10.4 Hz, J^2 = 4.7 Hz, 1H), 3.48 (dd, J^1 = 10.4 Hz, J^2 = 7.1 Hz, 1H), 3.36 (dd, J^1 = 16.1 Hz, J^2 = 9.2 Hz, 1H),

3.11 (dd, J^1 = 16.1 Hz, J^2 = 6.5 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.8, 132.0, 127.1, 125.2, 121.7, 112.4, 81.2, 34.6, 34.4, 15.0; HRMS (APCI, positive mode) *m*/*z* calculated for $C_{10}H_{10}Br_2O$ $[M]^+$ 305.9073, found: 305.9087.

Compound 2d. The general procedure was followed using **1d** (89.1 mg, 0.5 mmol), DCM (5 mL), glacial acetic acid (0.25 mL), DBU (7.5 μL, 10.0 mol%, related to **1d**) and then *N*-bromosuccinimide (294 mg, 1.65 mmol). After 15 minutes of reaction the product was purified by silica gel chromatography (hexanes/AcOEt = 98/2) to afford **2d** as a white solid (52.0 mg, 31% yield); m.p. = 69–71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.65 (s, 1H), 5.13–5.03 (m, 1H), 3.84 (s, 3H), 3.65 (dd, J^1 = 10.6 Hz, J^2 = 4.4 Hz, 1H), 3.54 (dd, J^1 = 10.6 Hz, J^2 = 7.5 Hz, 1H), 3.39 (dd, J^1 = 16.5 Hz, J^2 = 9.3 Hz, 1H), 3.17 (dd, J^1 = 16.5 Hz, J^2 = 6.7 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.6, 143.0, 130.3, 128.0, 114.0, 111.6, 81.5, 56.3, 37.2, 34.1, 22.1; HRMS (APCI, positive mode) *m*/*z* calculated for $C_{11}H_{13}BrO_2$ $[M]^+$ 256.0093, found 256.0092.

Compound 2e. The general procedure was followed using **1e** (210.3 mg, 1.0 mmol). After 3 hours of reaction the product was purified by silica gel chromatography (hexanes/AcOEt = 95/5) to afford **2e** as a white solid (206.1 mg, 56% yield); m.p. = 87–89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.51–7.46 (m, 3H), 7.42–7.38 (m, 2H), 7.33–7.31 (m, 2H), 5.16–5.09 (m, 1H), 3.68 (dd, J^1 = 10.4 Hz, J^2 = 4.3 Hz, 1H), 3.57–3.49 (m, 2H), 3.29 (dd, J^1 = 16.0 Hz, J^2 = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 156.0, 139.8, 136.3, 130.2, 128.8, 127.6, 127.2, 126.8, 122.9, 102.7, 81.8, 35.4, 34.0; HRMS (APCI, positive mode) *m*/*z* calculated for $C_{15}H_{12}Br_2O$ $[M]^+$ 367.9230, found: 367.9241.

Compound 2f. The general procedure was followed using **1f** (79.6 mg, 0.5 mmol), DCM (5 mL), glacial acetic acid (0.25 mL), DBU (7.5 μL, 10.0 mol%, related to **1f**) and then *N*-bromosuccinimide (294 mg, 1.65 mmol). After 24 hours of reaction the product was purified by silica gel chromatography (hexanes/AcOEt = 9/1) and then recrystallized in hexanes to afford **2f** as a white solid (107.6 mg, 68% yield); m.p. = 88–91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (s, 1H), 7.39 (s, 1H), 5.25–5.18 (m, 1H), 3.69–3.38 (m, 2H), 3.54 (dd, J^1 = 16.4 Hz, J^2 = 9.4 Hz, 1H), 3.31 (dd, J^1 = 16.4 Hz, J^2 = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 160.4, 136.1, 128.5, 127.7, 117.9, 105.7, 103.1, 82.4, 34.7, 33.7; HRMS (APCI, positive mode) *m*/*z* calculated for $C_{10}H_7Br_2NO$ $[M]^+$ 316.8869, found 316.8867.

Compound 2g. The general procedure was followed using **1g** (44.0 mg, 0.25 mmol), DCM (2.5 mL), glacial acetic acid (0.125 mL), DBU (4.0 μL, 10.0 mol%, related to **1g**) and then *N*-bromosuccinimide (147 mg, 0.825 mmol). After 6 hours of reaction the product was purified by silica gel chromatography (hexanes) and then recrystallized in hexanes to afford **2g** as a white solid (10.0 mg, 10% yield); m.p. = 87–93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.57 (s, 1H), 7.76 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 5.38–5.20 (m, 1H), 3.59 (dd, J^1 = 10.9 Hz, J^2 = 4.2 Hz, 1H), 3.42 (dd, J^1 = 10.9 Hz, J^2 = 5.4 Hz, 1H), 3.13 (dd, J^1 = 13.7 Hz, J^2 = 5.8 Hz, 1H), 2.92 (dd, J^1 = 13.7 Hz, J^2 = 7.4 Hz, 1H), 2.62 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 203.8, 170.1, 159.8, 140.2, 131.9, 128.2, 120.6, 110.0, 71.1, 34.0, 32.7, 26.8, 20.9; HRMS (APCI, positive mode) *m*/*z* calculated for $C_{13}H_{15}BrO_4$ $[M–H]^+$ 313.0070, found 313.0078.

Synthesis of compound 4a. A 10 mL one-neck round-bottom flask was charged with **2a** (92.7 mg, 0.25 mmol), DBU (45.0 μL, 0.3 mmol) and 2 mL of dry DMSO. After 20 hours at 70 °C the reaction mixture was diluted with 5 mL of DCM and extracted with water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford **4a** as a pale orange solid (37.0 mg, 51% yield); m.p. = 88–90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52 (d, *J* = 1.8 Hz, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 6.38 (d, *J* = 1.0 Hz, 1H), 2.49 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.9, 150.9, 131.8, 128.4, 122.0, 115.6, 104.1, 103.1, 14.1; HRMS (APCI, positive mode) *m*/*z* calculated for $C_9H_6Br_2O$ $[M + H]^+$ 290.8838, found 290.8838.

Synthesis of compound 5a. A 10 mL one-neck round-bottom flask was charged with **2a** (92.7 mg, 0.25 mmol), NaN_3 (24.4 mg, 0.375 mmol) and 2 mL of dry DMSO. After 4 days at 30 °C the reaction mixture was diluted with 5 mL of DCM and extracted with water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford **5a** as a white solid (62.6 mg, 75% yield); m.p. = 63–64 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42 (s, 1H), 7.22 (s, 1H), 5.10–5.03 (m, 1H), 3.60 (dd, J^1 = 13.2 Hz, J^2 = 4.1 Hz, 1H), 3.50–3.38 (m, 2H), 3.15 (dd, J^1 = 16.1 Hz, J^2 = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.9, 133.5, 129.1, 127.0, 112.9, 103.4, 82.1, 54.0, 33.4; HRMS (APCI, positive mode) *m*/*z* calculated for $C_9H_7Br_2N_3O$ $[M–N_2 + H]^+$ 305.8947, found 305.8940.

Conflicts of interest

There are no conflicts to declare.

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